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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,528	01/23/2002	Daryl W. Hochman	480000.1003c2U	6046

20601 7590 07/13/2005

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,528	HOCHMAN, DARYL W.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,25-29,33 and 35-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,25-29,33 and 35-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/27/04, 11/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114.

2. By Amendment filed November 29, 2004, claims 22-24, 30-32 and 34 have been cancelled; claims 21, 27-28, 35-38, 41 and 43 have been amended; and claims 46-55 have been newly added. Claims 21, 25-29, 33 and 35-55 are currently pending for prosecution on the merits.

Response to Arguments

3. Applicant's arguments with respect to claims 21, 23-31, 33 and 35-45 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 45 is rejected under 35 USC 112, first paragraph, because the specification while being enabling for a treatment composition comprising a loop diuretic or Na+K+2Cl-, does not reasonably provide enablement for the term "a cation chloride cotransporter antagonist to the central nervous system of the subject" (claim 45). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: 1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All the factors have been considered with regard to the claim, with the most relevant factors discussed below.

Nature of the Invention: All rejected claims are drawn to method of treating migraine headache in subjects with the administration of said compositions to the subject.

State of the Art: The art recognizes the treatment of migraine headache, cortical spreading depression and/or the treatment of migraine by controlling "visual aura" via administering furosemide.

Relative Skill of Those in the Art: The relative skill of those in pharmaceutical art is high.

Predictability of the Art: The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. Likewise, the physiological or pharmaceutical activity of preventing or treating migraine

headache, cortical spreading depression and other headache conditions and/or symptoms of such conditions prior to filling of the instant invention was an unpredictable art.

Breadth of Claims: The claims are very broad due to the vast number of possible compounds of that are described as being "a cation chloride cotransporter antagonist to the central nervous system of the subject". The breadth of claims encompass any compositions or agents having antagonist activity of Na+/HCO3- cotransporter, Na+/glucose cotransporter, Na+/bile acid cotransporter, Na+/H+ cotransporter, Na+/Pi cotransporter, Na+/myoinositol cotransporter, Na+/Sulfate cotransporter or K+Cl- cotransporter that can not determined by the skill artisan.

Guidance of the Specification:

In the instant case, given the unpredictability of the physiological or pharmaceutical activity of the claimed agent, the agent having "a cation chloride cotransporter antagonist to the central nervous system of the subject" in treating migraine headache is insufficient for enablement. The specification provides no guidance, in the way of enablement for that claimed agent other than furosemide, more broadly loop diuretic or Na+K+2Cl- cotransporter antagonist. The specification fails to provide sufficient information or guidance that all compounds having "a cation chloride cotransporter antagonist to the central nervous system of the subject" that are potentially suitable for the invention work similarly as to furosemide. Furthermore, numerous possible compounds that are suitable for the invention are not necessarily structurally related to each other, and the skill artisan would have not known that which compounds of the claimed compounds are capable of accomplishing the desired result of the claimed invention without undue amount of experimentation.

In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreschfiedl, 110 F. 2d 235, 45 USPQ 36 (CCPA 1940), vies this general rule: "it is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combination included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S.5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The Presence or Absence of Working Examples: As stated above, the instant specification only provides enabling disclosure for the activity of furosemide in inhibiting cortical spreading depression, treating migraine headache, and reducing "visual auras" of migraine (page 5, lines 1-25 of the instant specification).

The Amount of Experimentation Necessary: The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely

routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the agents "a cation chloride cotransporter antagonist to the central nervous system of the subject" that would be enabled in this specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 21, 27-28, 35-38, 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Mathew et al. (Neurology, 1996;46:1226-1230).

Mathew teaches use of acetazolamide and furosemide in combination with abortive antimigraine agents (e.g., ergotamine, DHE, or sumatriptan), prophylactic agents such as beta blockers, amitriptyline or methysergide and/or nonsteroidal anti-inflammatory agents for the treatment of chronic daily headache including migraine headache with or without aura in human (abstract; page 1226, column 2, para. 5 thru page 1228, column 1, para. 4 ; page 1228, column 2, para. 6 thru page 1229, column 1, para. 1; page 1229, column 2, para. 1). The reference discloses that said combination resulted "in the number of days of severe headache, reduced consumption of abortive agents, and overall improvement of quality of life".

Although Mathew is silent about the functional characteristic of Na+K+2Cl- (i.e., furosemide) in "capable of inhibiting Na+K+2Cl- cotransport in glial cells to the central nervous system", "blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system"; "produces modulation of the chloride concentration in extracellular space in the central nervous system", such characteristics or properties deems to be inherent to the of Na+K+2Cl- cotransporter antagonist such as furosemide. Therefore, the reference anticipates the claimed invention.

Since the interpretation of the instant claims allow for the inclusion of any other unspecified ingredient(s) even in major amounts in the anti-migraine treatment regimen (either coadministration or separate administration), the referenced administration of the acetazolamide and furosemide in combination with the antimigraine agents, prophylactic agents and/or nonsteroidal anti-inflammatory agents for the treatment of migraine headache with or without aura by "reducing the number of days of severe headache...overall improvement of quality of life" anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 25-26, 29, 33, 39-44, 47-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathew et al. (Neurology, 1996;46:1226-1230), and further in view of Levin (US 6432986) and Bentley et al. (US 6369094) and Becker et al. (US 5256687).

The teaching of Mathew has been discussed in above 35 USC 102(b) rejection.

Levin is being supplied as a reference to demonstrate the routine knowledge in the art of delivering anti-migraine agents by intranasal and transdermal or topical administration (column 36, lines 31-38; column 9, lines 7-17; column 41, lines 40-43); sustained release formulation, liposome formulation (column 31, lines 22-31); by implantation or therapeutic device (column 39, lines 3-62). Levin also teaches the use of divalproex sodium for the treatment of migraine headache (column 35, lines 31-32 and column 36, lines 6-7).

Bentley is being supplied as a reference to demonstrate the routine knowledge in the art of delivering anti-migraine agents in various dosage forms including oral, intracvernosal, parenteral (i.e., intracranially), transdermal, ocular and topical administration or controlled released and fast dispersion formulation (column 3, line 8 thru column 4, line 60).

Becker is being supplied as a reference to demonstrate the routine knowledge in the art of using mannitol as pharmaceutical excipient or carrier for furosemide (column 11, line 13).

The teaching of Mathew differs from the claimed invention in (i) the incorporation of a blood brain barrier permeability enhancer or hyperosmotic agent or solution (claims 25-26, 33, 39, 40 and 53, (ii) the use of divalprex sodium and (iii) the administration of said composition in

various dosage delivery systems including intransally, intracranially, transdermally, a sustained release formulation, liposome formulation, by implantation of a formulation or therapeutic device.

However, one having ordinary skill in the art would have known by the art-recognized routine knowledge (Levin Bentley and Becker) that determination of various dosage delivery system or dosage formulation including intranasal, intracranial or transdermal delivery or sustained release formulation, liposome formulation or by implantation or therapeutic device is well within the skill of artisan, especially in migraine therapy art. Furthermore, one having ordinary skill in the art would have expected that the incorporation of divalproex sodium would provide beneficial effect to the treatment of migraine headache. It is obvious to combine two or more compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980)*. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the incorporation of hyperosmotic agent or solution, Becker teaches the use of mannitol as well known secondary agent for furosemide formulation. Thus, one having ordinary skill in the art would have been motivated to combine the references and make such modification to increase the efficacy and extend the usage of furosemide containing composition by making suitable formulation for the claimed invention to accommodate patient's preference

and needs where the compliance could be improved with effective and well tolerated dosage regimen.

7. Claims 25-26, 33, 39-40, 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathew et al. (Neurology, 1996;46:1226-1230) in view of Read et al. (Cephalalgia, 1997, December, 17(8):826-832).

The teaching of Mathew has been discussed in above 35 USC 102(b) rejection.

Read teaches use of furosemide in non-reactive carrier or hyperosmotic agent such as saline solution, which is a loop diuretic with activity at the electroneutral Na+K+2CL-, in inhibiting regenerative cortical spreading depression in anaesthetized cats, wherein the mechanism of inhibition of cortical spreading depression activity by furosemide may be through alterations in cortical ion buffering capacity or inhibition of cell swelling in neurons or glia (abstract; page 826, column 1, para. 1-3 thru column 2, para. 1; page 837, column 2, para. 2). Read also teaches that the inhibition of cortical spreading depression is potentially useful for the treatment of migraine therapy (abstract; page 832, column 1, lines 7-11).

The teaching of Matthew differs from the claimed invention in the use of said Na+K+2Cl- as only agent that materially affect the basic and novel characteristic of the claimed invention. To incorporate such teaching into the teaching of Mathew, would have been obvious in view of Read who teaches the use of furosemide as potential agent for the treatment of migraine therapy. One having ordinary skill in the art would have expected as taught by Read that furosemide alone could be useful for the treatment of migraine therapy. One having ordinary skill in the art would have been able to make correlation between Matthew's teaching in the activity of furosemide in enhancing the efficacy of abortive antimigraine agent and Read's

teaching in using furosemide as a potential agent for the migraine therapy. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 21, 25-29, 33 and 35-55 are provisionally rejected under the judicially created doctrine of double patenting over claims 12-18 of copending Application No. 11/101,000. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the copending application and the instant application overlaps to each other. Since the instantly claimed "migraine headaches" falls under the term "neuropxychiatric disorder", the copending application makes obvious the instantly claimed composition.

Conclusion

9. No Claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
Patent Examiner
AU 1614